# Pre-operative Vitamin D and Calcium Administration in Patients Undergoing Thyroidectomy to Prevent Hypocalcemia: A Systematic Review and Meta-analysis of Randomized Controlled Trials M. Alhakami<sup>1,2</sup>; G. Bin Lajdam<sup>1,2</sup>; A. Ghaddaf<sup>1,2</sup>; <u>S. Alayoubi<sup>3</sup>; S. Alhelali<sup>4</sup>; M. Alshareef<sup>3</sup>; J. Alharbi<sup>5</sup></u> <sup>1</sup>College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia., <sup>2</sup>King Abdullah International Medical Research Center, Jeddah, Saudi Arabia., <sup>3</sup>Department of Otolaryngology-Head & Neck Surgery, King Abdulaziz Medical City, Jeddah, Saudi Arabia., <sup>4</sup>Collage of Medicine, Ibn Sina National Collage for Medical Studies, Jeddah, Saudi Arabia., <sup>5</sup>Head & Neck and Skull Base Health Center, King Abdullah Medical City, Makkah, Saudi Arabia.



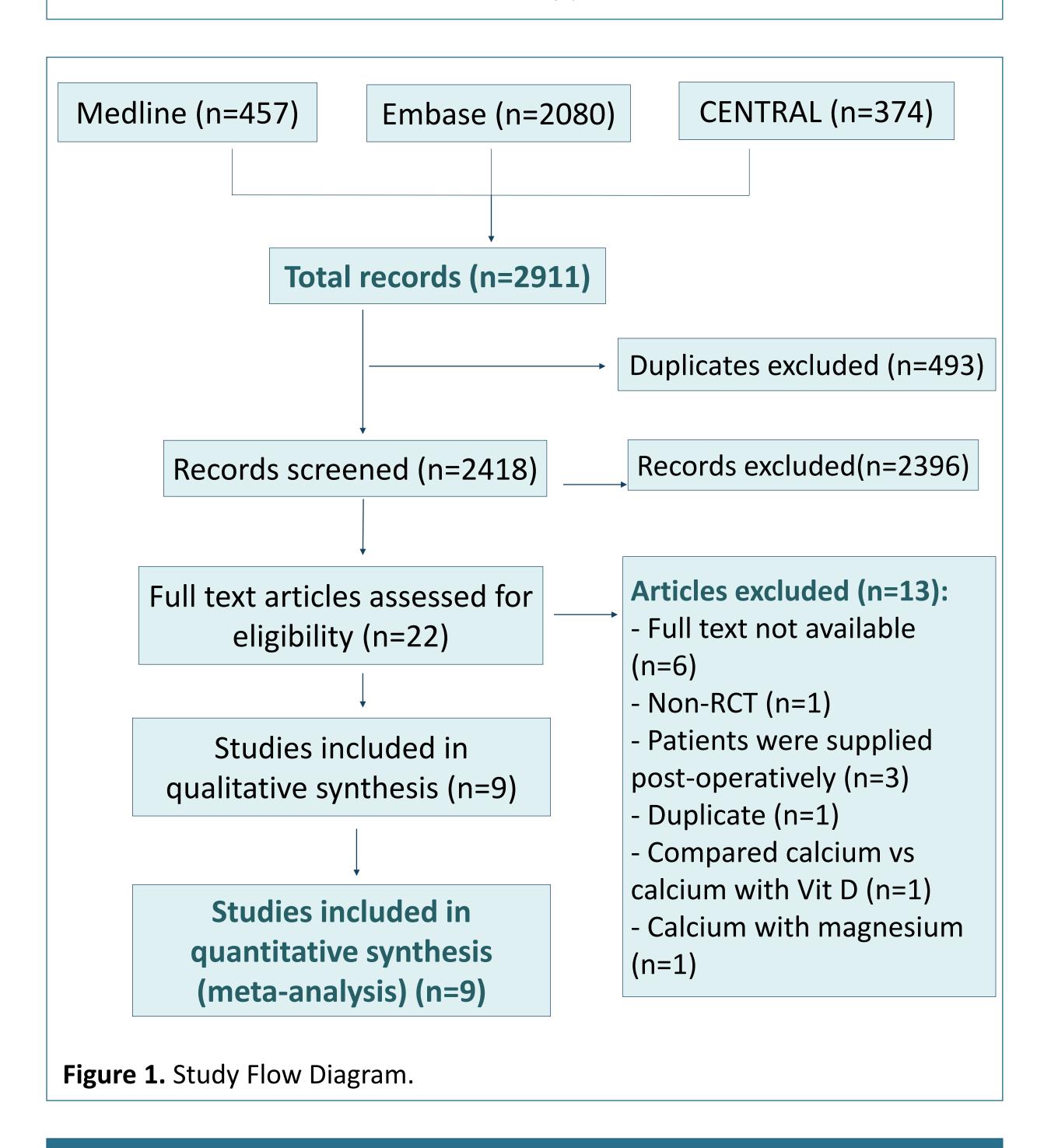
## Abstract

**Background:** Post-thyroidectomy hypocalcemia is a common complication that results in adverse neurological and cardiac symptoms. The use of calcium and vitamin D has been proposed as a pre-operative preventative strategy for this complication.

**Objective:** To assess whether pre-operative administration of calcium and vitamin D prevents post-operative hypocalcemia.

**Methods:** Computerized search in Medline, Embase, and CENTRAL databases was performed. Randomized controlled trials (RCTs) comparing pre-operative calcium and Vitamin D administration with either placebo or no intervention were included.

### Data analysis - Meta-analysis: Random-effects model. - Heterogeneity: I<sup>2</sup> and P-value of Chi<sup>2</sup> test. - **Significance level:** 95% with a P-value threshold < 0.05. - Quality assessment: Revised Cochrane Risk of Bias Tool. - Publication bias assessment: Not applicable.



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Study or Subgroup Eve Donahue 2021 Genser 2014 Jaan 2017 Ramouz 2020	1 12	Total E 38 111	Events 3	Total 44		IV, Random, 95% CI	IV, Random, 95% CI
Genser 2014 Jaan 2017	12		3	44	2 40/		
Jaan 2017		111		1.1	2.4%	0.39 [0.04, 3.56]	
	2	TTT	24	108	28.7%	0.49 [0.26, 0.92]	<b>_</b>
Ramouz 2020	3	30	12	30	8.8%	0.25 [0.08, 0.80]	
	2	50	8	50	5.2%	0.25 [0.06, 1.12]	
Rowe 2018	9	72	12	78	18.3%	0.81 [0.36, 1.81]	
Sasi 2022	12	41	19	42	35.0%	0.65 [0.36, 1.16]	— <b>—</b> — <b>—</b> — <b>—</b> —
Shonka 2021	1	23	1	24	1.6%	1.04 [0.07, 15.72]	
Total (95% CI)		365		376	100.0%	0.54 [0.38, 0.76]	•
Total events	40		79				
Heterogeneity: $Tau^2 = 0.00$	0; Chi <sup>2</sup> :	= 4.49,	df = 6	(P = 0.	61); $I^2 =$	0%	
Test for overall effect: Z =	3.50 (P	<b>P</b> = 0.00		0.01 0.1 1 10 10 Favours [Intervention] Favours [control]			

	Experim	iental	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Donahue 2021	4	38	4	44	3.5%	1.16 [0.31, 4.32]	
Genser 2014	7	111	15	108	7.5%	0.45 [0.19, 1.07]	
Jaan 2017	6	30	13	30	8.0%	0.46 [0.20, 1.05]	
Malik 2019	3	46	12	46	4.2%	0.25 [0.08, 0.83]	
Ramouz 2020	16	50	19	50	15.1%	0.84 [0.49, 1.44]	— <b>—</b> —
Rowe 2018	21	72	30	78	18.5%	0.76 [0.48, 1.20]	
Sasi 2022	22	41	20	42	20.0%	1.13 [0.74, 1.73]	
Sonnenberg 2021	38	130	39	116	23.1%	0.87 [0.60, 1.26]	
Total (95% CI)		518		514	100.0%	0.77 [0.60, 1.00]	•
Total events	117		152				
Heterogeneity: Tau <sup>2</sup>	,		,	7 (P =	0.18); I <sup>2</sup> =	= 31%	0.01 0.1 1 10 10
Test for overall effect: $Z = 1.97 (P = 0.05)$							Favours [Intervention] Favours [control]

**Results:** A total of 9 RCTs that enrolled 1079 patients were found eligible. Although post-operative laboratory hypocalcemia occurred less in patients who received pre-operative calcium and vitamin D, it was not found to be statistically significant (RR = 0.77, 95% CI: 0.60 to 1.00; P = 0.05). Mean post-operative calcium level was significantly higher in the intervention group (SMD = 0.10, 95% CI: 0.07 to 0.12; P=0.00001). The number of patients with symptomatic hypocalcemia was significantly lower in the intervention group (RR = 0.54, 95% CI: 0.38 to 0.76; P = 0.0005).

**Conclusion:** Administration of calcium and vitamin D pre-operatively achieves lower rates of post-thyroidectomy symptomatic hypocalcemia in comparison with placebo or no intervention.

## Introduction

- Hypocalcemia is the most common complication following thyroidectomy.
- Hypocalcemia may manifest as neurological and cardiac symptoms. - The use of calcium and vitamin D has been proposed as a preoperative preventative strategy.

#### **Figure 4.** Laboratory Hypocalcemia Meta-analysis.

	Experimental		Control				Mean Difference	Mean Difference	
Study or Subgroup	Mean			Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.1.1 Post-operative	day 1								
Donahue 2021	9.53	0.56	38	9.41	0.4	44	1.1%	0.12 [-0.09, 0.33]	
Genser 2014	8.3	0.52	111	8.14	0.56	108	2.5%	0.16 [0.02, 0.30]	
Jaan 2017	8.88	0.76	30	8.53	0.96	30	0.3%	0.35 [-0.09, 0.79]	
Ramouz 2020	8.93	0.1	50	8.85	0.09	50	36.3%	0.08 [0.04, 0.12]	
Sasi 2022	7.99	0.76	41	8.13	1.03	42	0.3%	, ,	
Subtotal (95% CI)			270			274	40.5%	0.09 [0.05, 0.12]	◆
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.91, df = 4 (P = 0.42); I <sup>2</sup> = 0%									
Test for overall effect:	Z = 4.2	77 (P <	< 0.000	01)					
1.1.2 Post-operative	-								
Genser 2014		0.14	111		0.18	108	27.6%	0.08 [0.04, 0.12]	*
Jaan 2017		0.72	30		0.76	30	0.4%	0.26 [-0.11, 0.63]	
Sasi 2022	8.17	0.77	41	8.11	1.04	42	0.3%	0.06 [-0.33, 0.45]	
Subtotal (95% CI)			182			180	28.3%	0.08 [0.04, 0.12]	•
Heterogeneity: $Tau^2 =$	,		,	-	P = 0.6	54); I <sup>2</sup> =	: 0%		
Test for overall effect:	Z = 3.3	81 (P =	= 0.000	1)					
1.1.3 Post-operative	day 3								
Donahue 2021	9.82	0.58	38	9.83	0.69	44	0.7%	-0.01 [-0.28, 0.26]	
Jaan 2017	8.97	0.7	30	8.78	0.74	30	0.4%	0.19 [-0.17, 0.55]	
Ramouz 2020	9.03		50		0.11	50	29.7%	0.13 [0.09, 0.17]	-
Sasi 2022	8.28	0.71	41	8.27	0.79	42	0.5%	0.01 [-0.31, 0.33]	
Subtotal (95% CI)			159			166	31.3%	0.13 [0.09, 0.17]	•
Heterogeneity: Tau <sup>2</sup> =	= 0.00; <b>(</b>	Chi² =	1.59, d	lf = 3 (I	P = 0.6	56); I <sup>2</sup> =	: 0%		
Test for overall effect:	: Z = 6.	14 (P <	< 0.000	01)					
Total (95% CI)			611			620	100.0%	0.10 [0.07, 0.12]	♦
Heterogeneity: Tau <sup>2</sup> =	= 0.00; (	Chi² =	9.24, d	lf = 11	(P=0	.60); I <sup>2</sup>	= 0%		
Test for overall effect:	Z = 8.4	49 (P <	< 0.000	01)		. *			–0.5 –0.25 0 0.25 0.5 Favours [Control] Favours [Intervention]
Test for subgroup differences: $Chi^2 = 2.84$ , $df = 2$ (P = 0.24), $I^2 = 29.7\%$									

#### **Figure 5.** Mean Calcium Levels Meta-analysis.

## **Primary Objectives**

- To assess the rate of laboratory hypocalcemia.
- To assess the rate of symptomatic hypocalcemia.
- To assess the mean postoperative calcium levels.

# **Methods and Materials**

- This systematic review was done according to a pre-specified protocol following Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). PROSPERO ID: CRD42022356363.

- **Population:** Adults 18 or above undergoing thyroidectomy.
- Intervention: Calcium, vitamin D, or both.
- **Comparison:** Placebo or no treatment.
- Outcomes: Symptomatic hypocalcemia, laboratory hypocalcemia, and mean calcium level.
- **Studies:** RCTs conducted in English.

### Search Strategy

- The following databases were searched: MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL).

## Results

#### **Characteristics of Included Studies**

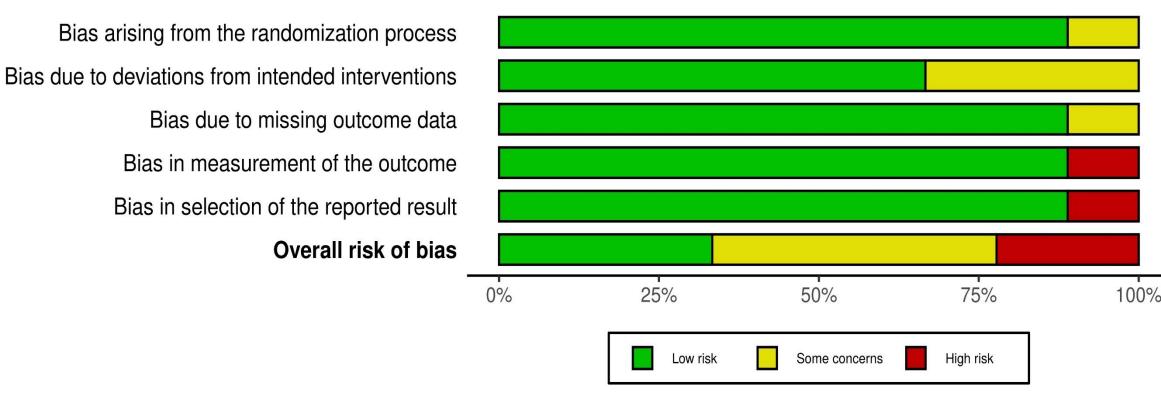
- Number of studies (fig.1): 9 RCTs.

- Total number of participants: 1079 participants.

- Study Arms:
- Intervention group: 541 (50.1%), control group: 538 (49.9%). - Mean age: 23.79 to 59.34 years.

- Gender distribution:

- Male: 251 (23%), female: 828 (77%).



### Figure 2. Risk of Bias Summary.

**Risk of Bias Assessment (fig.2)** - Low risk of bias: 3 RCTs. - Some concern: 4 RCTs.

## Discussion

- The mainstay preventive measure of post-thyroidectomy hypocalcemia is preserving parathyroid glands during surgery.

 Perioperative calcium and vitamin D supplementation was heavily studied. Recent study found that postoperative calcium and vitamin D administration did not reduce the risk of postoperative hypocalcemia.

- Our study showed a significant lower rate of symptomatic hypocalcemia and a higher mean postoperative calcium levels when vitamin D alone or in combination with calcium was administered preoperatively.

## Conclusions

- The preoperative administration of vitamin D and calcium resulted in lower rates of symptomatic hypocalcemia and a higher mean postoperative calcium levels.

- Although intervention group had lower occurrence of postoperative laboratory hypocalcemia, no statistically significant







## Contact

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